www.aassjournal.com
ISSN (Online)**: 2322 – 4479**
ISSN (Print)**: 2476–4981**

Editorial

www.AESAsport.com
Received: 01/02/2017
Accepted: 10/07/2017

SLC2A4 Polymorphisms Can Be a New Molecular Biomarker for Sports Genomics

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DEAR EDITOR

To date, most of the studies were conducted on the genetic SNPs of athletic performance. Angiotensin converting enzyme (ACE) insertion/ deletion and alpha- actinin-3 (ACTN3) R577X are the most widely analyzed polymorphisms in sports genomics (1, 2). Besides these, other SNPs are still under investigation, which are considered to have an important effect on athletic performance. But, due to the lack of new hypothesis in sports biology, studies are getting limited by time. Therefore, we need to evaluate new metabolic pathways to understand which factors are important for athletic performance.

Glucose is the most important carbon source and energy supply for almost every cell in our body. Its distribution to tissues through the blood and its transportation from the cell membrane is important for aerobic capacity of the cell. Besides, glucose transportation into muscles is important for normoglycemia. Skeletal muscle stores glucose as glycogen and also oxidizes it to produce energy following its transport step. All animal cells contain a group of membrane proteins involved in transporting glucose into the cell (3). This transportation is maintained by 13 different sugar transporter proteins, GLUT1-GLUT12 and HMIT (4). These sugar transporters display differences in their kinetics and respective substrate specificities, such that GLUT5 and probably GLUT11 are likely to be fructose transporters.

GLUT4 is highly expressed in adipose tissue and skeletal muscles, but these tissues also express a selective cohort of the other transporters. In skeletal muscles, GLUT1, GLUT5, and GLUT12 may significantly contribute to sugar uptake in addition to GLUT4 (5) whereas in adipose tissue, GLUT8, GLUT12 and HMIT are also involved in sugar uptake (6, 7).

In skeletal muscle cells, glucose uptake is carried out by facilitated diffusion, and this process depends on the presence of GLUT4 in the surface membrane. The main regulative sites/processes in this manner are: *1*) glucose delivery to muscles, *2*) glucose transport from membrane, and *3*) glucose utilization. When the cells are under rest, *GLUT1* expression is relatively low and muscle GLUT4 proteins reside within intracellular vesicles. Insulin stimulation and exercise acutely trigger GLUT4 protein transportation to the cell surface of muscle and adipose cells, independent of transcription or translation (8, 9). Under aerobic

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conditions, like endurance exercise; GLUT4 translocation from intracellular vesicles to the sarcolemma and T-tubules increase glucose transport. Researchers have reported the importance of *GLUT4* for muscle glucose uptake during electrical stimulation in *GLUT4* knockout (KO) mice in which muscle contractions has negligible effect on glucose uptake (10, 11). In addition to this, muscle glucose uptake is markedly reduced along with exercise tolerance in mice with muscle-specific *GLUT4* deletion during exercise (12). And also it is known that increased skeletal muscle *GLUT4* expression would also facilitate post-exercise glucose uptake and glycogen storage (13).

Recent studies showed that exercise increases the expression of GLUT4 mRNA and protein. The gene responsible for GLUT4 is *SLC2A4* (Gene ID: 6517), that is a member of the solute carrier family 2 (facilitated glucose transporter) member 4. It is located at 7p13 and has 11 exons. This gene has several SNPs in its promoter, exon, intron and UTR regions, which may have functional alterations in gene metabolism. Up to date, over 50 variations in the gene were reported. Of these, rs2654185, rs5412, rs5418 and rs5435 are the most functional SNPs in the gene.

To date, very limited studies were carried out in the terms of sports genetics, trying to associate athletic performance and *SLC2A4* polymorphisms. The G→A transition (rs5418) in *SLC2A4* promoter region was shown to alter *SLC2A4* expression. Although this variation is not located in the coding part and does not possess functional motifs in the protein, it may be very important in gene expression because it is very close to transcription start site (at 30 bp locus of *SLC2A4* promoter). Before, GG genotype of rs5418 was reported to have a lower amount of *SLC2A4* mRNA when compared to AA and AG genotypes (14). Xia *et al.* (2014) analyzed 102 top-level long-distance runners (53 men and 49 women) and compared them with 206 healthy controls (118 men and 88 women) in the northern Han Chinese population. Results of the study revealed that AA genotype and A allele of rs5418were associated with top-level endurance performance (15). The same authors also reported the high amount of GLUT4 protein in A allele carriers. But these studies are very limited to understand the effect of these SNPs on athletic performance.

Athlete- sedentary, national athlete- elite athlete studies and comparison of the related SNPs in athletes from different sports types will be very informative studies in the terms of sports genomics. Therefore, future analyses of *SLC2A4* polymorphisms and GLUT4 metabolism in athletes in different sports types will help to clarify the importance of the related SNPs in determining athletic performance.

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